

CLAIMS

1. A GLP-2 derivative comprising a lipophilic substituent attached to any one amino acid residue.

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2. A GLP-2 derivative according to claim 1 with the proviso that only if the substituent has an ω -carboxylic acid group or is an alkyl group can it be attached to the N-terminal or C-terminal amino acid residue of the parent peptide.

A 10 3. A GLP-2 derivative according to claim 1 ~~or 2~~, wherein the lipophilic substituent comprises from 4 to 40 carbon atoms, more preferred from 8 to 25.

A 15 4. A GLP-2 derivative according to ^{claim 1} ~~anyone of the preceding claims~~, wherein said lipophilic substituent is attached to said amino acid in such a way that a carboxyl group of the lipophilic substituent forms an amide bond with an amino group of the amino acid.

A 20 5. A GLP-2 derivative according to ^{claim 1} ~~anyone of the claims 1-3~~, wherein said lipophilic substituent is attached to said amino acid in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid.

A 25 6. A GLP-2 derivative according to ^{claim 1} ~~anyone of the preceding claims~~, wherein the lipophilic substituent is attached to the parent peptide by means of a spacer.

7. A GLP-2 derivative according to claim 6, wherein the spacer is an unbranched alkane α,ω -dicarboxylic acid group having from 1 to 7 methylene groups, preferably two methylene groups which form a bridge between an amino group of the parent peptide and an amino group of the lipophilic substituent.

8. A GLP-2 derivative according to claim 6, wherein the spacer is an amino acid residue except Cys, or a dipeptide such as Gly-Lys.

9. A GLP-2 derivative according to claim 8, wherein a carboxyl group of the parent peptide forms an amide bond with an amino group of Lys or a dipeptide containing a Lys residue,

and the other amino group of the Lys or a dipeptide containing a Lys residue forms an amide bond with a carboxyl group of the lipophilic substituent.

10.A GLP-2 derivative according to claim 8, wherein an amino group of the parent peptide
5 forms an amide bond with a carboxylic group of the amino acid or dipeptide spacer, and an amino group of the amino acid or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

10 11.A GLP-2 derivative according to claim 8, wherein a carboxyl group of the parent peptide forms an amide bond with an amino group of the amino acid or dipeptide spacer, and the carboxyl group of the amino acid or dipeptide spacer forms an amide bond with an amino group of the lipophilic substituent.

15 12.A GLP-2 derivative according to claim 8, wherein a carboxyl group of the parent peptide forms an amide bond with an amino group of Asp or Glu, or a dipeptide containing an Asp or Glu residue, and a carboxyl group of the spacer forms an amide bond with an amino group of the lipophilic substituent.

A 13.A GLP-2 derivative according to ^{claim 1} ~~any one of the preceding claims~~, wherein the lipophilic
20 substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

A 14.A GLP-2 derivative according to ^{claim 1} ~~any of claims 1-12~~, wherein the lipophilic substituent is
25 an straight-chain or branched alkyl group.

A 15.A GLP-2 derivative according to ^{claim 1} ~~any of claims 1-12~~, wherein the lipophilic substituent is
the acyl group of a straight-chain or branched fatty acid.

30 16.A GLP-2 derivative according to claim 15 wherein the acyl group is selected from the group comprising $\text{CH}_3(\text{CH}_2)_n\text{CO}-$, wherein n is 4 to 38, preferably $\text{CH}_3(\text{CH}_2)_6\text{CO}-$, $\text{CH}_3(\text{CH}_2)_8\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{10}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{12}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{14}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{18}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{18}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{20}\text{CO}-$ and $\text{CH}_3(\text{CH}_2)_{22}\text{CO}-$.

claim 1
 A 17.A GLP-2 derivative according to ¹any of claims 1-12, wherein the lipophilic substituent is an acyl group of a straight-chain or branched alkane α,ω -dicarboxylic acid.

18.A GLP-2 derivative according to claim 17 wherein the acyl group is selected from the group comprising $\text{HOOC}(\text{CH}_2)_m\text{CO}-$, wherein m is 4 to 38, preferably $\text{HOOC}(\text{CH}_2)_{14}\text{CO}-$, $\text{HOOC}(\text{CH}_2)_{16}\text{CO}-$, $\text{HOOC}(\text{CH}_2)_{18}\text{CO}-$, $\text{HOOC}(\text{CH}_2)_{20}\text{CO}-$ and $\text{HOOC}(\text{CH}_2)_{22}\text{CO}-$.

claim 1
 A 19.A GLP-2 derivative according to ¹any of claims 1-12, wherein the lipophilic substituent is a group of the formula $\text{CH}_3(\text{CH}_2)_p((\text{CH}_2)_q\text{COOH})\text{CHNH-CO}(\text{CH}_2)_2\text{CO}-$, wherein p and q are integers and p+q is an integer of from 8 to 40, preferably from 12 to 35.

claim 1
 A 20.A GLP-2 derivative according to ¹any of claims 1-12, wherein the lipophilic substituent is a group of the formula $\text{CH}_3(\text{CH}_2)_r\text{CO-NHCH}(\text{COOH})(\text{CH}_2)_2\text{CO}-$, wherein r is an integer of from 10 to 24.

claim 1
 A 21.A GLP-2 derivative according to ¹any of claims 1-12, wherein the lipophilic substituent is a group of the formula $\text{CH}_3(\text{CH}_2)_s\text{CO-NHCH}((\text{CH}_2)_2\text{COOH})\text{CO}-$, wherein s is an integer of from 8 to 24.

claim 1
 A 22.A GLP-2 derivative according to ¹any of claims 1-12, wherein the lipophilic substituent is a group of the formula $\text{COOH}(\text{CH}_2)_t\text{CO}-$ wherein t is an integer of from 8 to 24.

claim 1
 A 23.A GLP-2 derivative according to ¹any of claims 1-12, wherein the lipophilic substituent is a group of the formula $-\text{NHCH}(\text{COOH})(\text{CH}_2)_4\text{NH-CO}(\text{CH}_2)_u\text{CH}_3$, wherein u is an integer of from 8 to 18.

claim 1
 A 24.A GLP-2 derivative according to ¹any of claims 1-12, wherein the lipophilic substituent is a group of the formula $-\text{NHCH}(\text{COOH})(\text{CH}_2)_4\text{NH-COCH}((\text{CH}_2)_2\text{COOH})\text{NH-CO}(\text{CH}_2)_w\text{CH}_3$, wherein w is an integer of from 10 to 16.

claim 1
 A 25.A GLP-2 derivative according to ¹any of claims 1-12, wherein the lipophilic substituent is a group of the formula $-\text{NHCH}(\text{COOH})(\text{CH}_2)_4\text{NH-CO}(\text{CH}_2)_2\text{CH}(\text{COOH})\text{NH-CO}(\text{CH}_2)_x\text{CH}_3$, wherein x is an integer of from 10 to 16.

A 26.A GLP-2 derivative according to ^{claim 1} ~~any of claims 1-12~~, wherein the lipophilic substituent is a group of the formula $\text{-NHCH(COOH)(CH}_2)_4\text{NH-CO(CH}_2)_2\text{CH(COOH)NHCO(CH}_2)_y\text{CH}_3$, wherein y is zero or an integer of from 1 to 22.

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A 27.A GLP-2 derivative according to ^{claim 1} ~~any of the preceding claims~~ which has one lipophilic substituent.

A 28.A GLP-2 derivative according to ^{claim 1} ~~any one of claims 1-26~~ which has two lipophilic substituents.

A 29.A GLP-2 derivative according to ^{claim 1} ~~any one of the preceding claims~~, wherein the parent peptide is selected from the group comprising GLP-2(1-30); GLP-2(1-31); GLP-2(1-32); GLP-2(1-33); GLP-2(1-34) and GLP-2(1-35) or an analogue or a fragment thereof.

30.A GLP-2 derivative according to claim 29, wherein the parent peptide is selected from the group comprising GLP-2(1-35) or an analogue or a fragment thereof.

A 31.A GLP-2 derivative according to ^{claim 29} ~~any of the claims 29 and 30~~ wherein the designation analogue comprises derivatives wherein a total of up to ten amino acid residues have been exchanged with any α -amino acid residue.

A 32.A GLP-2 derivative according to ^{claim 1} ~~any of the preceding claims~~ wherein the parent peptide is selected from the group comprising $\text{Lys}^{20}\text{GLP-2(1-33)}$; $\text{Lys}^{20}\text{Arg}^{30}\text{GLP-2(1-33)}$; $\text{Arg}^{30}\text{Lys}^{35}\text{GLP-2(1-35)}$; $\text{Arg}^{30,35}\text{Lys}^{20}\text{GLP-2(1-35)}$; $\text{Arg}^{35}\text{GLP-2(1-35)}$; $\text{Arg}^{30}\text{Lys}^{34}\text{GLP-2(1-34)}$.

A 33.A GLP-2 derivative according to ^{claim 1} ~~any one of the preceding claims~~, which is selected from the group consisting of

$\text{Lys}^{20}(\text{N}^{\epsilon}\text{-tetradecanoyl})\text{GLP-2(1-33)}$;

$\text{Lys}^{20,30}\text{-bis}(\text{N}^{\epsilon}\text{-tetradecanoyl})\text{GLP-2(1-33)}$;

$\text{Lys}^{20}(\text{N}^{\epsilon}\text{-tetradecanoyl})\text{Arg}^{30}\text{GLP-2(1-33)}$;

Arg³⁰Lys³⁵(N^ε-tetradecanoyl)GLP-2(1-35);
 Arg^{30,35}Lys²⁰(N^ε-tetradecanoyl)GLP-2(1-35);
 Arg³⁵Lys³⁰(N^ε-tetradecanoyl)GLP-2(1-35);
 Arg³⁰Lys³⁴(N^ε-tetradecanoyl)GLP-2(1-34);
 5 Lys²⁰(N^ε-(ω-carboxynonadecanoyl))GLP-2(1-33);
 Lys^{20,30}-bis(N^ε-(ω-carboxynonadecanoyl))GLP-2(1-33);
 Lys²⁰(N^ε-(ω-carboxynonadecanoyl))Arg³⁰GLP-2(1-33);
 Arg³⁰Lys³⁵(N^ε-(ω-carboxynonadecanoyl))GLP-2(1-35);
 Arg^{30,35}Lys²⁰(N^ε-(ω-carboxynonadecanoyl))GLP-2(1-35);
 10 Arg³⁵Lys³⁰(N^ε-(ω-carboxynonadecanoyl))GLP-2(1-35); and
 Arg³⁰Lys³⁴(N^ε-(ω-carboxynonadecanoyl))GLP-2(1-34).

claim 1

A 34.A pharmaceutical composition comprising a GLP-2 derivative according to ~~any of the~~ ^{claim 1} preceding claims and a pharmaceutically acceptable vehicle or carrier.

15 35.Use of a GLP-2 derivative according to any of the claims 1-33 for the preparation of a medicament.

20 36.Use of a GLP-2 derivative according to any of the claims 1-33 for the preparation of a medicament with protracted effect.

37.Use of a GLP-2 derivative according to any of claims 1-33 for the preparation of a medicament with protracted effect for the treatment of obesity.

25 38.Use of a GLP-2 derivative according to any of claims 1-33 for the preparation of a medicament with protracted effect for the treatment of small bowel syndrome.

39.A method of treating obesity in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a GLP-2 derivative according to ^{claim 1} ~~any one of the claims 1-33~~ together with a pharmaceutically acceptable carrier.

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